## Remarks

Applicants have amended claim 29 to depend from only one claim. Claims 34 and 43 have been amended to correct minor typographical errors. Claims 25-48 are pending. Support for amendments to the claims made herein can be found throughout the specification as filed. Thus, no new matter has been added.

## I. Objections to the Claims

The Examiner has objected to Claim 29 as being in improper form. Applicants have amended the claim herein to depend from claim 27 only. Accordingly, this objection has been obviated and should be withdrawn. Additionally, the Examiner has objected to Claims 34 and 43 due to the lack of periods at the end of the claims. Applicants have amended these claims herein to correct this informality. Accordingly, this objection has been obviated and should be withdrawn.

## II. Rejection of the Claims Under 35 USC § 101/112

Claims 25-47 are rejected under 35 USC §§ 101 & 112, first paragraph for allegedly lacking a patentable utility. *See* pages 4-6 of Paper No. 20060321. The Examiner appears to discount the asserted utilities listed for Clone ID HFXHC41 (corresponding to SEQ ID NO:48) as based solely on sequence homology to CD44 and cartilage link protein. Specifically, the Examiner states,

> Sequence alignment performed at the USPTO indicates that the SEQ ID NO. 48 share 34% identity over CD 44 (AAB00792) and 45% identity over cartilage linked protein (CAA35462)... Without a high degree of sequence similarity, it is not deemed reasonably to support one skilled in the art whether the biochemical activity of the polypeptide would be the same as that of such similar known protein. *See* Paper No. 20060321, page 5.

The Examiner further states, "Applicants list a number of possible uses for CD44 disclosed in the application, such as its role for leukocyte migration or in the regulation of tumor metastasis (page 13). But Applicants fail to assert a specific utility for the claimed polypeptide encoded by SEQ ID NO: 48."

Applicants respectfully disagree and traverse. The asserted utilities listed in the specification for HFXHC41 are not based solely on sequence homology to CD44 and

cartilage link protein. The specification teaches that HFXHC41 contains two link domains. A link domain is defined as "a hyaluronan(HA)-binding region found in proteins of vertebrates that are involved in the assembly of extracellular matrix, cell adhesion, and migration" *See* Specification, page 14, paragraph [0041]. The specification goes on to provide a schematic representation of the conserved link domain and provides the link domains present in HFXHC41 as SEQ ID NOS: 80 and 81. Based on sequence similarity, including the presence of these link domains, HFXHC41 is described in the specification as a novel homolog of human cartilage link protein, and other hyalaronan binding domain proteins (including CD44). *See* Specification, page 14, paragraph [0040] through page 16, paragraph [0044]. Furthermore, the specification teaches that HFXHC41 is "expressed primarily in adult brain, multiple sclerosis, Human Manic Depression Tissue, Spinal Cord, Hippocampus, Substantia Nigra, frontal cortex, and to a lesser extent, in placenta." *See* page 16, paragraph [0045]. The asserted utilities listed in the specification for HFXHC41 are therefore based not only on sequence homology to cartilage link protein, but also on the presence of two link domains that have been demonstrated to be involved in HA binding and tissue distribution.

Furthermore, Applicants demonstrate below that the claimed invention is indeed supported by an asserted specific and substantial utility that is credible. For example, post filing date publications have confirmed the activities of HFXHC41 as first described in the instant application.[1] As described in Hirakawa *et al.* and Spicer *et al.* (submitted herein as references AW and AX, respectively), expression of sequences corresponding to HFXHC41 (referred to therein as "brain link protein-1 [BRAL1]" or "HAPLN2") is expressed predominantly in adult brain. Spicer *et al.* also provide a gene comparison of HFXHC41 with the other known members of the HA binding link family (including HAPLN1 [cartilage link protein-1]) including an alignment of the conserved link domains. The expression profile of BRAL1 was further characterized in Oohashi *et al.* (submitted herein as reference AY). BRAL1 mRNA was detected in neuronal cells of the cerebellum, spinal cord, olfactory bulb, cerebral cortex, hippocampus,

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[1] Applicants point out that post-filing date scientific papers, such as the paper discussed herein, may be used to corroborate Applicants' asserted utility. Legal precedent for the use of post-filing date references in this manner can be found in In re Brana, where the Federal Circuit stated that:

> The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. In re Marzocchi, 439 F.2d at 224 n.4, 169 U.S.P.Q. (BNA) at 370 n.4. 51 F.3d 1560, 1567, 34 U.S.P.Q.2D (BNA) 1436 (Fed. Cir. 1995).

and brainstem. BRAL1 protein was localized in the extracellular matrix of the white matter in the central nervous system and specifically localized at nodes of Ranvier. Furthermore, Oohashi et al. reports that "our biochemical and immunohistochemical observations strongly suggest that Bral1 binds to HA, as expected from its homology to Crtl1 and other HA-binding molecules" [Crlt1 = cartilage link protein-1].

Moreover, the present specification teaches that "elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival." *See*, page 17, paragraph [0048]. This statement is supported by the observation of Oohashi *et al.* that "[t]he characteristic accumulation of Bral1 on axons at the nodes of Ranvier indicates that Bral1 may play a pivotal role in the HA-associated matrix for neuronal conduction in the mature CNS." *See*, Oohashi *et al.*, page 52, right column, first full paragraph.

Furthermore, the specification teaches that the compositions of the claimed invention "are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions." More specifically, the specification states, "the uses include, but are not limited to the detection, treatment, and/or prevention of... schizophrenia." *See*, pages 17-18, paragraph [0048]. Nomoto *et al.* (submitted herein as reference AZ) report that:

> The brain- and nerve-tissue specificity displayed by *BRAL1* and *BCAN* marks its abnormal form as a potential candidate for involvement in neurological diseases. Among the human phenotypic mutations mapped to this region, schizophrenia 9 (SCZD9; OMIM No. 604906; ref. 16) is an allele with such potential. Recently, a genome-wide scan for schizophrenia susceptibility loci in 22 extended families with high rates of schizophrenia provided highly significant evidence for such loci at chromosome 1q21-q23, with a maximum heterogeneity logarithm of the likelihood of linkage (Lod) score of 6.50... *See*, page 27, right column, third paragraph.

The authors further describe the identification of repetitive CA repeats within the BRAL1 and BCAN genes and provides analysis of polymorphisms in the identified regions, concluding, "[t]he highly informative CA-repeat marker HNCA2 presented here would facilitate the investigation of the possibility that BRAL1 and BCAN genes may be involved in inherited schizophrenia." *See*, page 29, last sentence.

Applicants submit that, as corroborated by the above mentioned references, compositions corresponding to HFXHC41 (e.g., antibodies that bind the claimed polypeptides) may be useful, for example, in the detection, treatment, and/or prevention of diseases and conditions, such as neurodegenerative disease states, behavioral disorders, or inflammatory conditions including, but not limited to, schizophrenia. Applicants point out that the specification does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. See M.P.E.P. § 2107.02 (I) at 2100-34. All that is required of Applicants is that there be a *reasonable* correlation between the biological activity and the asserted utility (*see* Nelson v. Bowler, 626 F.2d at 857).

According to the Utility Examination Guidelines, the test for specificity is whether an asserted utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention, such as use of a complex machine for landfill. *See*, Utility Examination Guidelines. The disclosed utilities for HFXHC41 polypeptides discussed above are specific, in that not every protein may be used to, for example, to generate antibodies for diagnosing, treating and/or preventing schizophrenia. Consequently, the skilled artisan would most certainly not consider such a use to be a "throw-away utility" such as landfill.

Moreover, the disclosed utilities for HFXHC41 polypeptides discussed above are substantial and credible, as "the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." *See*, Revised Interim Utility Guidelines Training Materials, page 6. Pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 USC § 101. *See*, Nelson v. Bowler, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980); *See also,* M.P.E.P. §2107.01(III). It is well-established that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and satisfies the utility requirement. *Id.* Accordingly, the utilities asserted by Applicants are clearly substantial and credible.

In view of the above, Applicants respectfully submit that the presently claimed invention possesses specific, substantial, credible utilities which constitute patentable utilities under 35 USC § 101. Thus, even assuming, *arguendo*, the Examiner had established a *prima facie*

showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by sufficient evidence to lead one skilled in the art to conclude that at least one of the asserted utilities is more likely than not specific, substantial, and credible. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Examiner has rejected claims 24-47 under 35 U.S.C. § 112, first paragraph, alleging that one skilled in the art clearly would not know how to use the claimed invention since the claimed invention is not supported by either a specific, substantial, credible utility, asserted utility or a well established utility. *See* Paper No. 20060321, page 6. In view of the arguments presented above in response to the rejection under 35 USC § 101, Applicants submit that the claims are supported by a specific, substantial, and credible asserted utility, and thus adequately teach how to use the invention. Accordingly, it is requested that the instant rejection be reconsidered and withdrawn.

## III. Rejection Under 35 USC § 112, First Paragraph

Claims 25, 27-38 are rejected under 35 USC §112, first paragraph for allegedly lacking written description. Specifically, the Examiner states,

> This is a new matter rejection. Although Applicants has provided detailed indications for support for the amended claims, the specification does not meet the limitations of claim 25. In particular, the specification does not provide support for an antibody binding at least 30 or 50 contiguous amino acid residues specific for SEQ ID NO:48.
> (Paper No. 20060321, page 7).

Applicants respectfully disagree and traverse. The specification as filed provides support for antibodies binding at least 30 or 50 contiguous amino acids. In particular, the specification states, "Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1". *See* pages 219-220, paragraph [0661]. Furthermore, the specification states, "polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y". *See* page 96, paragraph [0253]. Polypeptide fragments are provided in the specification as "about 20, 30,

40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, and ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes." *See* pages 89-90, paragraph [0236].

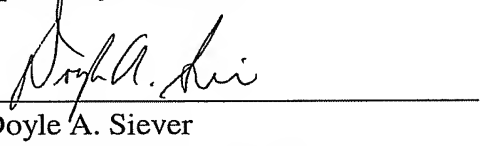
Accordingly, Applicants respectfully submit that one skilled in the art would reasonably conclude that Applicants had possession of the claimed invention. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

## Conclusion

Applicants respectfully request that the above-made remarks and amendments be entered and made of record in the file history of the instant application. In view of the foregoing remarks, Applicants believe that this application is now in condition for further examination. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the allowance of this application. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: June 30, 2006

Respectfully submitted,

By 

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